National Institute for Public Health
and the Environment
*Ministry of Health, Welfare and Sport*

# Update human MPR-air formaldehyde

RIVM Letter report xxxxxx
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# Colophon



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Contact:

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[ FORMTEXT ]

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# Synopsis

**Update human MPR-air formaldehyde**

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# Summary

# 1 Introduction

The Maximum Permissible Risk (MPR; in Dutch: Maximum Toelaatbaar Risico, MTR) is the regulatory environmental quality criterion for the protection of human health and the environment within Dutch environmental policy. The human MPR-air is the estimated maximum concentration in air that will not cause adverse health effects in the general population upon lifetime exposure. The MPR-air is also denoted as the Tolerable Concentration in Air (TCA) (in Dutch: Toelaatbare Concentratie in Lucht, TCL).

For formaldehyde (methanal) the current MPR-air equals 10 $\mu g/m^3$ (RIVM 2011). As explained in RIVM (2010) this MPR-air is the year-average value already in use for many years by the Ministry of Infrastructure and Environment. The derivation of this value, however, is unknown (RIVM 2010). In addition to the year-average value of 10 $\mu g/m^3$ the Ministry uses a short-term value for indoor air of 120 $\mu g/m^3$ as a 30-minutes average. The latter value dates back to 1978, when it was derived by an interdepartmental working-group under the former Ministry of Public Health and the Environment. This indoor air limit value of 120 $\mu g/m^3$ was included in the Particle Board Decree (Spaanplaat-Besluit) under the Dutch Food and Commodities act (Warenwet) in 1986.

Formaldehyde inhalation toxicity was re-evaluated by the RIVM in 1995 within the scope of the soil intervention value project on behalf of the former Ministry of Physical Planning and the Environment. This led to a proposed MPR-air (TCA) of 1.2 $\mu g/m^3$ (RIVM 1995). The latter value, however, was never officially adopted by the Ministry. Instead, the year-average value of 10 $\mu g/m^3$ has remained in place as the official value.

In recent years several organisations have again evaluated formaldehyde health effects, especially with a view to exposure via indoor air. Within REACH a joint evaluation was done by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) and RIVM (ECHA 2013, 2015). This resulted in placing formaldehyde on the REACH Community rolling action plan (CoRAP) for substance evaluation (ECHA 2015). As part of this REACH process a draft evaluation has been prepared of the general population DNEL (Derived No Effect Level ≈ MPR-air) as proposed by the REACH registrant for formaldehyde. Specific issues related to the REACH process for formaldehyde were the update of the CLP based on the accumulated health effects data (human and animal) and indoor air exposure assessment.

For the current update existing evaluations by US-EPA (2010), BfR (2006), Health Canada (2005), WHO (2010), NTP (2014) and the US National Research Council (NRC 2011, 2014) were used as source documents. In addition, the various documents as recently prepared under REACH were used.

Synopisis
Section 2 provides an overview of current general population limit values as derived by various organisations. Section 3 provides background information on the formaldehyde concentrations as measured in indoor air and outdoor air in various countries. The main focus in the current report is updating the toxicological evaluation for the inhalation route; this is presented in section 4. Finally, in section 5 the recent $MPR_{air}$ is derived.

# 2 Existing general population limit values

Based on past evaluations sensory irritation (of nose, throat, eyes), possible effects on lung function and cancer of the upper respiratory tract (especially the nasopharynx) can be identified as the critical health effects for human inhalation exposure to formaldehyde. Much research has been performed to elucidate the mechanism through which formaldehyde produces tumours in the upper airways. For deriving general population health-based limit values the most plausible dose response relation for the tumour formation needs to be determined from these data. In past evaluations by RIVM and others (WHO, BfR, ANSES), a non-linear dose response (threshold) was concluded to be the most likely option based on available evidence. Preventing the relevant precursor event of local cytotoxicity in the upper airways would also preclude any risk on tumour formation, it was concluded. Sensory irritation as occurring after exposure to formaldehyde via air was taken as a surrogate for local cytotoxicity and thus the maximum concentration not producing sensory irritation was deemed to simultaneously be safe with regard to the carcinogenicity endpoint.

Current MPR-air and the Dutch indoor air limit value

As already mentioned in section 1, the basis for the current MPR-air of 10 µg/m$^3$ as a year-average is unknown. The current short-term limit value of 120 µg/m$^3$ for indoor air was derived from a human study by Rader (1974) in which an unknown number of volunteers in a medical anatomical preparation room reported subjective complaints (odour, irritation of eyes, nose and throat) upon acute exposure to 240 µg/m$^3$ (exposure time not reported). At 120 µg/m$^3$ no response was found in this study (Gezondheidsraad 1984). This result was the basis for the Dutch indoor air 30-minutes maximum of 120 µg/m$^3$ as derived in 1978 by an interdepartmental working-group of the former Ministry of Public Health and the Environment. Later, in 1984, the Dutch Health Council (Gezondheidsraad) proposed the following limit values for outdoor air based on the same study:

- Ceiling (based on 30-minutes average): 120 µg/m$^3$
- 98-percentile (based on 24-hour average): 40 µg/m$^3$
- 95-percentile (based on 24-hour average): 30 µg/m$^3$

The lower values for the 24-hour average were calculated based on datasets for measured outdoor air concentrations which showed spread over time within the usual minimum sampling time of 24 hours. The Dutch Health Council points out that the assumed distribution for outdoor air will not readily apply to indoor air but the 30-minutes ceiling should be the same for both indoor and outdoor air (Gezondheidsraad 1984). These proposals by the Gezondheidsraad have not been officially adopted by the former Ministry of Public Health and the Environment but possibly the current MPR-air of 10 µg/m$^3$ as a year-average was chosen by taking into account available information on the distribution of formaldehyde outdoor air concentrations over time.

Since the period when the current $MPR_{air}$ was established a number of other general population limit values have been derived by various national and international organisations. Appendix 1 provides an overview of the most relevant evaluations.

Table 1 lists the values as described in Appendix 1.

| ***Table 1: General population inhalation reference values for formaldehyde*** **Organisation** | **Year** | **Reference value** | **Averaging time** | **Basis** |
|---|---|---|---|---|
| Former Ministry of Public Health and the Environment (Netherlands) | 1979 | 120 µg/m$^3$ (indoor air) | 30 minutes | NOAEL 120 ug/m3 for subjective complaints (odour, irritation of eyes, nose and throat) from human volunteer study by Rader et al. (1974) (exposure time not reported) |
| Gezondheidsraad | 1984 | Proposed for outdoor air:<br>-120 µg/m3 (ceiling)<br>- 40 µg/m3 (98 percentile)<br>- 30 µg/m3 (95 percentile) | <br>30 minutes<br>24 hours<br>24 hours | Idem |
| RIVM | 1995 | 1.2 µg/m$^3$ (proposed) | Chronic | NOAEL of 120 ug/m3 from acute human volunteer studies (unspecified) and from 26-weeks study in monkeys (Rusch et al. 1983) |
| ATSDR | 1999 | 50 µg/m3 | 14 days | Minimal LOAEL of 0.4 ppm (0.48 mg/m$^3$) for mild eye, nose, and throat irritation in some human subjects in volunteer study by Pazdrak et al. (1993) (exposure for 2 hours) |
| ATSDR | 1999 | 35 µg/m3 | 15-365 days | NOAEL of 0.98 ppm (1.18 mg/m3) for clinical signs of nasopharyngeal irritation (hoarseness and nasal congestion and discharge) and lesions in the nasal epithelium (squamous metaplasia and hyperplasia) in Cynomolgus monkeys exposed for 22 hours/day, 5 days/week for 26 weeks (Rusch et al. 1983). |
| ATSDR | 1999 | 10 µg/m3 | Chronic (>365 days) | Minimal LOAEL of 0.24 ppm (0.289 mg/m3) for histological changes (loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia replacing the columnar epithelium) in nasal tissue specimens from a group of 70 workers employed for an average 10.4 years (range 1–36 years) in a |

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|---|---|---|---|---|
| | | | | chemical plant that produced formaldehyde and formaldehyde resins for impregnating paper (study by Holmstrom et al. 1989c). |
| WHO air quality guidelines | 2000 | 100 µg/m$^3$ (outdoor air) | 30 minutes | Signs of irritation of nose and throat above this level in healthy subjects (volunteer studies) (unspecified) |
| Health Canada | 2005 | 123 µg/m$^3$ (indoor air) | 1 hour | NOAEL and LOAEL of 615 and 1,230 µg/m3 respectively, based on eye irritation in healthy subjects in study by Kulle et al. (1993) with exposure for 3 hours |
| Health Canada | 2005 | 50 | 8-hour | Epidemiological studies on effects on lung function/asthma in children after chronic exposure:<br>-NOAELs in two studies 10-29 µg/m3 and 30-49 µg/m3<br>-non-significant increase of risk at 50 to 59 µg/m3 (OR 1.2)<br>-significantly increased risk at 60 µg/m3 (OR 1.39, $p<0.05$)<br>The risk of cancer was concluded to be negligible at formaldehyde concentrations sufficiently low to prevent local irritation and inflammatory responses in the upper airways |
| BfR | 2006 | 120 µg/m$^3$ | Unspecified | Estimated NOAEL for sensory irritation in humans is 0.1 ppm (0.12 mg/m3) based on chamber studies and occupational data (unspecified) |
| OEHHA | 2008 | 50 µg/m$^3$ | 1 hour | $BMCL_{05}$ for eye irritation of 0.44 ppm (530 µg/m3) based on the human volunteer study by Kulle et al. (1993) (exposure for 3 hours) (NOAEL 0.5 ppm; LOAEL 1 ppm) |
| OEHHA | 2008 | 9 µg/m$^3$ | 8 hours (repeated) | NOAEL 0.09 mg/m3 from occupational study by Wilhelmsson and Holmstrom (1992) with effects on the upper airways, including nasal obstruction and discomfort, lower airway discomfort, and eye irritation in workers exposed to a mean formaldehyde concentration of 0.26 mg/m3 five days/week (40 hours/week); referent group exposed to 0.09 mg/m3; average exposure period 10 years (range 1-36 years) |
| OEHHA | 2008 | 9 µg/m$^3$ | chronic | Idem |
| WHO | 2010 | 100 µg/m$^3$ | 30 minutes | NOAEL 0.6 mg/m3 for eye blink response, obtained from the |

| | | | | |
|---|---|---|---|---|
| | | | (ceiling, not to be exceeded during any 30 minutes period) | volunteer study by Lang et al. (2008) (exposure for 4 hours) |
| US-EPA (Draft) | 2010 | 20-84 µg/m$^3$ (candidate RfCs) | Not specified | Two cross-sectional epidemiology studies that evaluated sensory irritation in residents of mobile and conventional homes, i.e. Ritchie and Lehnen (1987) with an NOAEL of 60 µg/m3 and Hanrahan et al.(1984) from which a BMCL10 was calculated of 84 µg/m3. |
| US-EPA (Draft) | 2010 | 3.4-13 (candidate RfCs) | Not specified | Various non-cancer endpoints: induction of asthma and atopy, pulmonary function, reproductive effects |
| | | | | |
| ANSES | 2011 | 94 µg/m$^3$ | 1 hour | 1 hour REL as derived by OEHHA (1999) adopted |
| ANSES | 2011 | 10 µg/m$^3$ | chronic | Chronic reference value ATSDR (1999) adopted [1,2] |

[1] Actual indoor air quality guidelines values proposed for France based on this reference value can be found at: [ HYPERLINK "https://www.anses.fr/fr/system/files/AIR2011sa0123.pdf" ]
[2] The implementation of the French indoor air quality guidelines for chronic exposure to formaldehyde involves a phased approach with an interim guideline of 30 µg/m3 applying from 1-1-2015 onwards and a value of 10 µg/m3 from 1-1-2023 onwards. ([ HYPERLINK "https://www.anses.fr/fr/system/files/AIR2011sa0123.pdf" ])

Almost all of the values in Table 1 are based on sensory irritation as seen in studies in humans. Exceptions are the 8-hour limit value of 50 µg/m$^3$ derived by Health Canada (2005) and the candidate RfC's of the US-EPA developed for the induction of asthma and atopy, effects on pulmonary function and reproductive effects.

As already explained, in most limit value derivations sensory irritation was considered a surrogate for local cytotoxicity. Preventing cytotoxicity from occurring would also protect against carcinogenicity due to the existence of a threshold in the action by formaldehyde in the upper airways (RIVM 1995; Health Canada 2005; BfR 2006; OEHHA 2008; WHO 2010; ANSES 2011).

A complete updated evaluation of all in the scientific information on formaldehyde carcinogenicity and associated information on the mode of action including genotoxicity is provided by US-EPA (2010). This resulted in a quantification of formaldehyde cancer risks for nasopharyngeal cancer, Hodgkin lymphoma and leukemia based on human data, yielding unit risks (per ppm lifetime exposure) for extra cancer incidence of $1.1x10^{-2}$, $1.7x10^{-2}$ and $5.7x10^{-2}$, respectively. US-EPA also provides an in depth discussion of the biologically-based dose response model (BBDR) developed by Conolly et al. (2004) for formaldehyde human cancer risk assessment based on the nasal tumours as found in rat studies. The conclusion by US-EPA is that due to model uncertainties the human cancer risk estimates obtained by applying this model cannot be characterised as a plausible upper bound cancer risk estimate in the low dose range. Instead US-EPA opts for linear extrapolation based on two Points of Departure (POD) derived using the BBDR model, i.e. an extra risk of 0.5% and an extra risk of 1%. Linear extrapolation from these PODs led to unit risks of $1.2x10^{-2}$ per ppm lifetime exposure (for POD 0.5%) and $2.2x10^{-2}$ (for POD 1%), based on animal data (US-EPA 2010).

REACH (2012)

Within REACH the lead registrant proposed a general population DNEL (Derived No-Effect Level) based on the German occupation limit of 0.3 ppm (370 µg/m$^3$). Using an assessment factor of 3 would lead to a general population DNEL of 0.1 ppm (120 µg/m$^3$). In the Draft Substance Evaluation Report (SEV) as prepared by the Dutch member state competent authority (RIVM 2012) this DNEL was discussed and provisionally accepted for preliminary risk evaluation.

As to the carcinogenic effect after inhalation of formaldehyde, within REACH the registrant concluded that the DNEL was driven by effects on the upper respiratory tract and thus took into consideration the development of nasal tumours in rats. The occurrence of tumours was considered the result of chronic proliferative processes and the genotoxicity of formaldehyde was deemed to play no or at most a minor part in its carcinogenic potential. Cell proliferation is caused by cytotoxic irritation by formaldehyde, but data on cytotoxic irritation of the respiratory tract are not available for humans. However, the database for sensory irritation to the eye, a more sensitive parameter, could be used for DNEL derivation (RIVM 2012).

# 3 Concentrations in indoor and outdoor air

Formaldehyde concentrations are higher in indoor air than in outdoor air. This is due to indoor emission from sources such as composite wood products in furniture, floorings and panel boards, and from household products such as glues, permanent press fabrics, carpets, paints and coatings. The emissions and indoor air concentrations are highest when these materials or products are new. The draft SEV (RIVM 2012) provides a comprehensive compilation of reported formaldehyde concentrations in indoor air from different European countries. For the Dutch situation the data from Mediterranean countries are less relevant because levels in these countries are lower, probably due to a higher ventilation level in homes in these countries.

Below available information on concentrations in air is briefly summarised. Only the major studies are included (no full literature review).

## 3.1 Indoor air

### *3.1.1 Private houses*

In the Netherlands, TNO determined week-average concentrations in 358 houses, i.e. in the kitchen and one other room containing chipboards or plywood (van Dongen and Vos 2007). The measurements were performed during the heating-season.

***Table 2: Week-average formaldehyde concentration in kitchens and other rooms in µg/m³(van Dongen and Vos 2007)***

| Room | Formaldehyde concentration* (µg/m³) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | N | mean | SD | P05 | P50 | P95 | Min | Max |
| Kitchen | 359 | 12.6 | 1.6 | 6.3 | 12.6 | 25.1 | 1.0 | 79.4 |
| Other rooms | 360 | 12.6 | 2.0 | 1.0 | 12.6 | 25.1 | 1.0 | 39.8 |

* Concentrations recalculated from the $^{10}$log values given in the report and rounded off

As part of the German German longitudinal environmental survey 2003–2006 (GerES IV), formaldehyde was measured through passive samplers for one week in bedrooms of a randomly selected population of children and teenagers.

***Table 3: Week-average formaldehyde concentration in bedrooms of children and teenagers in µg/m³ in Germany (UBA 2008)***

| Formaldehyde concentration* (µg/m³) | | | | | | |
|---|---|---|---|---|---|---|
| N | Mean | P10 | P50 | P95 | P98 | Max |
| 586 | 25.7 | 13.2 | 23.5 | 47.7 | 58.3 | 68.9 |

Kirchner et al. (2007) and WHO (2010) summarize the week-average concentrations measured by the French Observatory on Indoor Air Quality during a large monitoring campaign in 567 randomly selected dwellings between 2003 and 2005. The median concentration, 95th percentile and maximum value of formaldehyde in bedrooms (n = 554) were 19.6, 46.7 and 86.3 µg/m$^3$ respectively.

More recent concentration measurements in France were carried in 27 apartments and 5 houses that were part of a special buildings energy programme. The reported mean annual concentrations for the apartments/houses were 17.7 µg/m$^3$ (standard deviation 7.5) with a range of 5.3-41.9 µg/m$^3$ (Derbez et al. 2015).

For the UK, Raw et al. (2004) report measurements of formaldehyde in the bedrooms of 833 homes located throughout England, carried out around the year 2000.

***Table 4: Three day-average formaldehyde concentrations (µg/m$^3$) in bedrooms in England (Raw et al. 2004)***

| **Formaldehyde concentration (µg/m$^3$)** | | | | | | |
|---|---|---|---|---|---|---|
| **N** | **Geometric mean** | **P10** | **P50** | **P95** | **Min** | **Max** |
| 833 | 22.2 | 9.8 | 24.0 | 61.2 | 1 | 171 |

These investigators found a clear effect of the building-date of the home with concentrations gradually rising in homes built from the 1960's onwards and with homes built during the 1990's reaching about three times the concentrations present in pre-1960's homes.

The finding that indoor air concentrations are highest in new homes or newly furnished homes has led to several investigations into the relevant exposure sources for the increased concentrations in new homes. Salthammer et al. (2010) describe laboratory measurements in a small test house in which low-emitting materials were used. Initially a concentration of 22 µg/m$^3$ was found, considered to be due to emission from common building materials (e.g. wallpaper). After introduction of carpet including carpet adhesive, and a sideboard made of lacquered particle board into the test house, concentrations of up to 69 µg/m3 were found.

In a study in Austria, Tappler et al. (2014) investigated the influence of having a mechanical air ventilation system on indoor air quality in 62 new low-energy homes with a controlled living-room heat recovery ventilation system and in a control group of 61 new traditionally built houses. Formaldehyde concentrations were measured twice, i.e. at 3 months after the residents had moved in and one year later (sampling time not reported). At the first measuring-time the mean concentration in the energy-efficient houses was 30 µg/m$^3$ (standard deviation 18 µg/m3) with a 95-percentile of 53 µg/m$^3$. In the traditional houses the mean was 41 µg/m$^3$ (standard deviation 17 µg/m$^3$) with a 95-percentile

of 67 µg/m$^3$. One year later measured mean concentrations were lower by about 20-25% in both types of houses (Tappler et al. 2014).

### 3.1.2 *Public buildings*

Formaldehyde concentrations have also been determined in public buildings, including classrooms and kindergartens. The EU's Joint Research Centre measured one-week average concentrations in public buildings (offices, schools or similar microenvironments) in 10 cities throughout Europe, finding mean concentrations from 13.9 to 22.9 µg/m$^3$ (total number of measurements 131) (Bruinen de Bruin et al. 2008).

In their review Mandin et al. (2012) present results of measurements, carried out in 401 classrooms in 108 schools located in 6 French cities during the year 1999. Concentrations ranged from 4 to 100 µg/m$^3$ with a mean value of 27 µg/m$^3$ (sampling time not reported). They also present results for 50 Parisian kindergartens studied between 1999 and 2001, both in winter and in summer (n = 222), with indoor formaldehyde concentrations ranging from 1.5 to 56 µg/m$^3$ with a median value of 14 µg/m$^3$.

Fromme et al. (2008) determined 5 hour-average concentrations in 91 classrooms in southern Bavaria in Germany in the winter of 2004/2005 and also in 76 classrooms in the summer of 2005. The median concentration in winter was 12.4 µg/m$^3$ (maximum 46.1 µg/m$^3$) and in summer 15.0 µg/m$^3$ (maximum 72.4 µg/m$^3$). WHO (2010) present formaldehyde concentrations measured in European kindergartens by the EU's Joint Research Centre between 2004 and 2007 (n = 57), the results showing a range from 1.5 to 50 µg/m$^3$, with an arithmetic mean of 17.4 µg/m$^3$ (sampling time not reported).

### 3.1.3 *Mobile homes*

Relatively high formaldehyde concentrations may be present in mobile homes due to high loading rates per m$^3$ of wood-based materials in combination with a low ventilation rate. This was already reported in the 1960's. The problem regained attention in the aftermath of the hurricane Katrina in the USA, when survivors living in trailers experienced health complaints, which were thought to be due to the presence of formaldehyde in indoor air. Salthammer et al. (2010) cite measurements in a limited number of trailers as used after Katrina, with one series in 519 trailers/mobile homes showing concentrations of in the range 3 to 590 ppb (3.6 to 708 µg/m$^3$) and some further measurements in 4 trailers having steady-state concentrations ranging from 378 µg/m$^3$ to 926 µg/m$^3$. As Salthammer et al. (2010) suggest, given the known influence of temperature and relative humidity on formaldehyde release from wood products, the hot and humid climate in the US region where Katrina occurred may well have contributed to the elevated formaldehyde concentrations.

## 3.2 Outdoor air

### 3.2.1 *General information*

The presence of formaldehyde in outdoor air is due to both natural and anthropogenic sources. Forest fires, animal wastes, microbial products of biological systems and emissions from plants are natural sources of formaldehyde. Anthropogenic sources are combustion processes, including exhaust from diesel- and gasoline-powered vehicles. In addition to direct emission there is indirect production by atmospheric photochemical oxidation by sunlight of hydrocarbons (notably methane and isoprene) or other formaldehyde precursors that have been released from combustion processes (Health Canada 2000). NTP (2010) indicates that there are data suggesting that outdoor formaldehyde levels due to secondary formation may be larger than levels from direct emissions. Tago et al. (2005) found that secondary formation of formaldehyde by photochemical reactions accounted for as much as 80% and 50% in summer and winter, respectively, at two sites in Japan, one urban and one rural.

In the atmosphere photo-oxidative degradation of formaldehyde also occurs. Reaction with the hydroxyl radical is the most important photo-oxidation process in the degradation of formaldehyde (NTP 2010). Formaldehyde half-lives in outdoor air can vary considerably under different conditions. Based on hydroxyl radical reaction rate constants, the atmospheric half-life of formaldehyde has been calculated to be between 7.1 and 71.3 hours. Formaldehyde is highly soluble in water and will transfer into clouds, precipitation, and surface water. WHO (2002) noted that formaldehyde has a washout ratio (concentration in rain/concentration in air) of 73,000, and thus is expected to be efficiently scavenged from the atmosphere by precipitation . Estimated atmospheric residence times for several U.S. cities ranged from 0.3 hours under conditions typical of a rainy winter night to 250 hours under conditions typical of a clear summer night (WHO 2002).

As pointed out by Salthammer (2012, 2013) the increasing use of biofuels in vehicles leads to higher levels of formaldehyde in ambient air in areas where there is much traffic.

### 3.2.2 *Reported concentrations*

IARC (2006) provides a comprehensive review of formaldehyde outdoor concentrations based on data published before the year 2000. For remote, unpopulated areas levels ≤1 µg/m$^3$ are reported. Outdoor air concentrations of formaldehyde in urban environments are more variable and depend on local conditions, with a usual range of 1 to 20 µg/m$^3$. For urban air in areas with heavy traffic or during severe atmospheric inversions the range can be up to 100 µg/m$^3$. As noted, these indications are based on data from before the year 2000.

Health Canada (2000) calculated the distribution of formaldehyde concentrations for outdoor air based on a large number of measurements (n=2818) of the 24-average concentration at four urban sites and four suburban sites in Canada carried out in the period 1990-1998. The result was a mean of 3.3 µg/m$^3$ (median 2.8 µg/m$^3$; 75$^{th}$ percentile 4.1 µg/m$^3$; 95$^{th}$ percentile 7.3 µg/m$^3$, 97.5$^{th}$ percentile 9.1 µg/m$^3$).

As part of the campaign to measure levels of formaldehyde in indoor air in French homes, Kirchner et al. (2007) also determined outdoor concentrations (1-week averages). For 529 homes throughout France they report a median concentration of 1.9 µg/m$^3$ (10th percentile 1.5 µg/m$^3$, 95th percentile 3.6 µg/m$^3$) (Kirchner et al. 2007; Mandin et al 2012).

Bruinen de Bruin et al. (2008) report 1 week-average concentrations in at outdoor work locations in 11 European cities (including Arnhem and Nijmegen in the Netherlands). The total number of measurements was 70. The mean concentration was 1.5 µg/m$^3$ (standard deviation 1.0 µg/$^3$; 95th percentile 3.4 µg/m$^3$).

Possanzini et al. (2002) determined diurnal fluctuations in formaldehyde concentrations in urban air in downtown Rome by measuring hourly concentrations on sunny and wind-calm days from 8.00 am until 22.00 pm during June and July 1994-1996 and during January- March 1995-1997. Hourly concentrations ranged from 7 to 28 ppb (8.6 – 34.4 µg/m$^3$) during summer and from 7 to 20 ppb (8.6 – 24.6 µg/m$^3$) during winter. In summer the contribution of photochemical formation was up to 80% at noon whereas in winter this was maximally around 35%.

Tang et al. (2009) reviewed available data with a special focus on China. The overall mean concentration in seven Chinese cities in 732 samples was 11.7 µg/m$^3$. The authors conclude that China's large cities have formaldehyde levels similar to cities in other developing countries such as Egypt, Mexico, and Brazil, but significantly higher than those of large cities in developed countries like Japan, Sweden and Canada. One of the studies included in this review was that by Pang and Mu (2006) who measured formaldehyde at a location in Bejing in 1 hour-samples taken from 8 until 20.00 hour, each day, in the winter of 2004/2005 and the spring, summer and autumn of 2005. The overall mean 1-hour concentration in winter was 4.2 µg/m$^3$ ± 2.8 µg/m$^3$ (range 1.1-12.1), in spring 14.5 µg/m$^3$ ± 8.7 µg/m$^3$ (range 1.9-45.8), in summer 19.5 µg/m$^3$ ± 8.9 µg/m$^3$ (range 2.6-52.9) and in autumn 15.8 µg/m$^3$ ± 9.7 µg/m$^3$ (range 3.7-45.6). For 4-15 days diurnal variation (8.00-20.00 hour) in 1 hour-concentrations were calculated, showing ranges of mean concentrations from about 3 to 7 µg/m$^3$ (winter), 11 to 16 µg/m$^3$ (spring), 14 to 26 µg/m$^3$ (summer) and 8 to 18 µg/m$^3$ (autumn). The elevated concentrations in spring, summer and autumn were ascribed to photooxidative formation (out of VOC) during these seasons (estimated contributions 71-78%). This was confirmed by a high correlation of the measured concentrations during these seasons with ozone concentrations. A high correlation with CO concentrations in winter was considered to indicate that formaldehyde in this period predominantly derived from direct emission from vehicles (Pang and Mu 2006).

Lü et al. (2010) measured formaldehyde concentrations in spring, summer, autumn and winter at an urban site with heavy traffic in Liwan and an urban site close to a residential area in Wushan. Liwan and Wushan are cities in Guangzhou province in China. During the day 2-3 hour samples were taken and during the night 12 hour samples were taken. The concentrations ranges were 0.18-11.2 µg/m$^3$ in spring, 3.30-21.4 µg/m$^3$ in summer, 2.18-5.78 µg/m$^3$ in autumn and 1.74-9.87

µg/m$^3$ in winter. In spring, summer and autumn concentrations during the night tended to be lower than during the day, maximally by a factor of 2. During winter concentrations during the night tended to be higher than during the day.

Salthammer (2013) is his review of available data on formaldehyde concentrations in ambient air concludes that in urban regions in northern and central Europe and in the United States, average values between 5 and 15 ppb (6 and 18 µg/m$^3$) are typical. The much higher concentrations reported for Asian and South American megacities especially in summer are due to formation in photosmog in the presence of reactive organic compounds such as alkenes. For such cities with high photochemical air pollution Salthammer indicates typical average formaldehyde concentrations of 20 ppb-30 ppb (24-36 µg/m$^3$) with peaks of 40-50 ppb (48-60 µg/m$^3$). Introduction of biofuels for automobiles in Rio de Janeiro, Brazil, led to very high concentrations of formaldehyde in air (averages above 120 µg/m$^3$) in 2004. Improved engine technology has led to some reduction of these levels (to around 35 µg/m$^3$ in 2009) (Salthammer 2013).

Morknoy et al. (2010) determined concentrations of formaldehyde in ambient air in 24-hour samples taken at five roadside locations with much traffic in Bangkok during July 2007 to April 2008. Concentrations were in the range from 5.14 to 17.2 µg/m$^3$ (average 11.53 µg/m$^3$). Three hour-samples were also taken at different time points during the day and night, showing mean concentrations during the day of 22-24 µg/m$^3$ and during the night of 13-16 µg/m$^3$. As to seasonal variation clearly lower concentrations (threefold lower) were found during the rainy season compared to the cool dry and the summer seasons. This indicates wash out. Good correlation with both ozone and CO indicated that both photoxidative formation of formaldehyde and direct emission from vehicles contributed to the concentration in ambient air.

# 4 Update of the toxicological evaluation

Based on the toxicological profile of formaldehyde and the existing evaluations as reviewed in appendix 1 to the present report, two effects can be identified as critical for MPR-air derivation:

1. Sensory irritation of the upper airways and the eyes
2. Carcinogenicity

These two effects are linked in that most existing evaluations aimed at derivation of a reference value for air (Gezondheidsraad 2003; WHO 2000, 2010, BfR 2006; Mandin et al. 2009, 2012) concluded that protection against sensory irritation of the upper respiratory tract (and eyes) would also protect against the carcinogenic action by formaldehyde in the upper airways. Sensory irritation was considered a suitable proxy for local cytotoxicity; the latter was considered to play a crucial role in tumour formation by formaldehyde in the upper airways.

Below the two critical effects will be discussed (in paragraphs 4.1 and 4.2 respectively). For formaldehyde carcinogenicity in the upper airways the information on the mechanism (mode of action) as presented by Gezondheidsraad (2003), US-EPA (2010), RAC (2012), IARC (2012) and NRC (2011, 2014) is important for reaching an updated conclusion on how to quantitatively assess the possible cancer risk posed by the chemical at environmentally relevant concentrations. This mode of action information includes data on genotoxicity, protein-DNA cross-link (DPX) formation, local cytotoxicity and cell proliferation. The biologically based model developed by Conolly et al. (2004) aimed at human cancer risk assessment for inhalation exposure to formaldehyde based on the animal bioassay results, is also taken into consideration. The discussion aims to provide an updated answer to the question of whether nonlinear (threshold) or linear (non-threshold) extrapolation is appropriate given the current weight of evidence.

In addition to the findings in animal and humans on the carcinogenic action by formaldehyde in the upper airways, some evidence exists for a systemic carcinogenic action by formaldehyde, specifically leukemia. This will also be addressed in paragraph 4.2.

## 4.1 Sensory irritation of the upper airways and the eyes

Irritation of the nose, throat and eyes after inhalation of formaldehyde has been observed in many studies, experimental ones as well as observational and occupational ones. As explained in chapter 2, the current 30-minutes MPR-air of 120 µg/m$^3$ is based on the result of a human study by Rader (1974) in which an unknown number of volunteers in a medical anatomical preparation room reported subjective complaints (odour, irritation of eyes, nose and throat) upon acute exposure to 240 µg/m$^3$ for an unknown period. At 120 µg/m$^3$ no response was found in this study (Gezondheidsraad 1984). Various other organisations have established acute reference values for general

population exposure (indoor or outdoor) based on selected individual volunteer studies. See section 2 for an overview.

As explained in Section 2, within REACH the registrant has proposed a general population DNEL (Derived No-Effect Level) of 100 µg/m3. To the German occupation limit of 0.3 ppm (370 µg/$m^3$) an assessment factor of 3 was applied, leading to a value of 0.1 ppm (120 µg/$m^3$). This value was rounded down to 100 µg/$m^3$, in agreement with WHO (2010). This is a 30-minutes ceiling value that should not be exceeded during any 30 minute period throughout the day.

In the REACH registration dossier on formaldehyde, the results of two volunteer studies, i.e. Lang et al. (2007) and Müller et al. (2013), are highlighted as providing support for the proposed DNEL of 100 µg/$m^3$. The study by Lang et al. (2007) was also used by the WHO for deriving an updated indoor air quality guideline of 100 µg/$m^3$.

The study by Lang et al. (2007) included 21 human volunteers (11 males, 10 females) who were exposed according to 10 different exposure scenarios for 4 hours per day on 10 consecutive days. Some scenarios included short-term peak exposures whereas in others ethyl acetate was used as a masking agent. Endpoints evaluated consisted of conjunctival redness, blinking frequency, nasal flow and resistance, pulmonary function, and reaction times. In addition subjective ratings of discomfort were recorded and the influence of personality factors on the subjective scoring was determined. The examinations were carried out pre-, during and/or post-exposure. No effect on nasal flow and resistance, pulmonary function, and reaction times was found. Blinking frequency and conjunctival redness were significantly increased by short-term peak exposures of 1.0 ppm (1.2 mg/$m^3$) superimposed on a baseline exposure to 0.5 ppm (0.6 mg/$m^3$). Results of the subjective ratings indicated eye and olfactory symptoms at ≥0.3 ppm (≥0.4 mg/$m^3$). When taking into account personality factors as a covariate, the level of 0.3 ppm (0.4 mg/$m^3$) was no longer an effect level but 0.5 ppm (0.6 mg/$m^3$) with peaks of 1.0 ppm (1.2 mg/$m^3$) was. The authors concluded that the results indicated eye irritation as the most sensitive parameter. Minimal objective eye irritation was found at a level of 0.5 ppm (62 mg/$m^3$) with peaks of 1 ppm (1.2 mg/$m^3$). The NOAEL for subjective and objective eye irritation due to formaldehyde exposure was 0.5 ppm (0.6 mg/$m^3$) after constant exposure without peaks and 0.3 ppm (0.4 mg/$m^3$) with peaks of 0.6 ppm (0.7 mg/$m^3$) (Lang et al. 2007).

The same research group carried out a similar volunteer study in male workers (n=42), subdivided into a group considered hyposensitive to nasal irritation and into a group considered hypersensitive. Individual sensitivity to nasal irritation was determined using subjective pain perception as induced by nasal application of carbon dioxide as the indicator. The subjects were exposed for 4 hours per day for 5 days in a randomised schedule to a formaldehyde concentration of 0 ppm (control), 0.5 and 0.7 ppm (610 and 860 µg/$m^3$) and to 0.3 (370 µg/$m^3$) ppm with peak exposures of 0.6 ppm (740 µg/$m^3$) and to 0.4 ppm (490 µg/$m^3$) with peak exposures of 0.8 ppm (980 µg/$m^3$), respectively. Peak exposures were carried out four times per day over 15 minutes' periods.

Examinations before and after exposure: subjective rating of symptoms and complaints, conjunctival redness, eye-blinking frequency, self-reported tear film break-up time and nasal flow rates. In addition, the influence of personality factors on the volunteer's subjective scoring was examined. No effect occurred on the conjunctival and nasal parameters. No differences between hypo- and hypersensitive subjects were found. Statistically significant differences were noted for olfactory symptoms, especially for the 'perception of impure air'. These subjective complaints were more pronounced in hypersensitive subjects. The authors conclude the NOAEL for subjective and objective eye irritation was 0.5 ppm (610 µg/m$^3$) (constant exposure level) and 0.3 ppm (370 µg/m$^3$) with peaks of 0.6 ppm (740 µg/m$^3$) for the scenario with short-term peak exposures (Müller et al. 2013).

As indicated in appendix 1, WHO (2010) based its indoor air quality guideline on the NOAEL of 0.5 ppm (0.6 mg/m$^3$ for the eye blink response from the volunteer study by Lang et al. (2008). An assessment factor of 5 derived from the standard deviation of nasal pungency (sensory irritation) thresholds, was applied, leading to a value of 120 µg/m$^3$, which was rounded down to 100 µg/m$^3$. This may be considered a consensus reference value for sensory irritation. As also pointed out by WHO (2010) this value is a 30-minutes value, which should not be exceeded during any 30 minute period throughout the day. The same limitation as to averaging time already applied to the Dutch short-term MPR-air of 120 ug/m$^3$ as established in 1978. It is important to consider possible fluctuations over time in formaldehyde concentrations when comparing this reference value with indoor or outdoor concentrations measurements. In measuring concentrations sampling times of 24 hours or longer are mostly used. Concentration fluctuations within this time period may occur potentially leading to the situation where the 24 hour average remains below the reference value but over a shorter period the value was in fact exceeded. This problem was already dealt with by the Gezondheidsraad in 1984 in its proposal for Dutch outdoor air quality limits for formaldehyde (see also section 5).

## 4.2 Carcinogenicity

### *4.2.1 Classification*

IARC (2012)

Formaldehyde has been classified by IARC (2012) as a proven human carcinogen (Group 1), based on *sufficient evidence* for cancer of the nasopharynx and for leukaemia in humans from epidemiological studies. This classification was based on:

- a strong association between exposure to formaldehyde and cancer of the nasopharynx in the industrial NCI-cohort (consisting of about 25000 workers in 10 plants in the USA);
- positive associations for the same tumour observed in case-control studies, in particular those of larger sizes and higher-quality exposure assessments;
- a positive association in epidemiological studies in humans between exposure to formaldehyde and sinonasal cancer;

- evidence for the induction of leukaemia in two industrial worker cohort studies, from occupational studies of professionals (i.e. proportionate mortality studies in embalmers, funeral parlour workers, pathologists and anatomists) and from a nested case-control study of embalmers.

IARC concluded that animal experiments provide *sufficient evidence* for the carcinogenicity of formaldehyde. IARC notes that concerning the leukaemias in epidemiological studies within the Working-Group a small majority viewed the evidence as *sufficient* but the minority viewed the evidence as *limited* only (IARC 2012).

RAC (2012)

Based on evaluation of the human epidemiological data and also taking into account the IARC evaluation as published in 2012, the RAC classified formaldehyde as Carc. 1B according to CLP criteria. Rationale for this classification:

- a positive association between exposure to formaldehyde and the frequency of nasopharyngeal cancers observed in one industrial cohort (the industrial NCI-cohort);
- a causal interpretation for this association is plausible but some uncertainties remain and chance, bias or confounding cannot not be ruled out with reasonable confidence;
- supporting evidence for nasopharyngeal cancer coming from case-control studies (especially Vaughan et al. 2000);
- for sinonasal cancers overall weak evidence from some case-control studies;
- strong evidence for cancers of the upper respiratory tract (URT) from animal bioassays.

In its conclusion on the overall strength of evidence, the RAC took into account the remaining uncertainties. RAC concluded there to be *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* from animal studies. Taking into account the significant, but overall small increase in tumours [n=10 in the critical human epidemiology study, i.e. the industrial NCI-cohort study] and considering the remaining uncertainties, RAC considered that the strength of evidence was not sufficient to justify classification in carcinogenicity category 1A.

As to the possible carcinogenicity at distant (systemic) sites, RAC (2012) concluded:

- animal studies (inhalation, oral) do not provide evidence of a carcinogenic effect at distant sites;
- some epidemiological studies have found increased rates of leukaemia, but the findings are not consistent across studies and the effect lacks biological plausibility. Slightly increased leukaemia rates were found among embalmers, pathologists and anatomists but not among industrial workers, which suggests the possibility of confounding factors (RAC 2012).

NTP (2014)

Within the US the National Toxicology Program formaldehyde was classified as a known human carcinogen. The evidence was strongest for nasopharyngeal cancer. For this type of cancer and for sinonasal cancers, the available population- and occupation-based case-control

studies were considered more informative than the cohort studies because these cancer types are rare (annual incidence of less than 1 per 100,000 in most parts of the world). For nasopharyngeal cancer the multi-center case-control study by Vaughan et al. (2000) was considered especially informative because it had the largest number of cancer cases in formaldehyde-exposed individuals, and the analysis was stratified by histological subtype and used several different measures of exposure. In this and in other case-control studies increased risk for nasopharyngeal cancer was found among individuals classified as having the highest formaldehyde exposure. The excess of nasopharyngeal cancer mortality in the NCI cohort of industrial workers was cited as providing further evidence for a causal link for this cancer type in humans and inhalation exposure to formaldehyde. Although some epidemiological studies did not find an association between formaldehyde exposure and nasopharyngeal cancer, the overall consistency of the findings was judged to argue against their being attributable to chance. For sinonasal cancer there were consistent findings of increased risk in population-based case-control studies, it was concluded, and limited evidence from cohort studies (with the latter being qualified as less informative for this rare tumour type). For leukaemias (all types combined) increased risks were judged to be present in all of the professional studies and some of the industrial cohort studies. Among studies that evaluated subtypes, the strongest associations were observed for myeloid leukaemia.

In conclusion, NTP (2014) classified formaldehyde as a known human carcinogen based on consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration). These findings could not be explained by chance, bias, or confounding, it was concluded (NTP 2014).

NRC (2014)

The US National Research Council (NRC 2014) carried out an independent assessment of all human epidemiology data, all animal data and all mode-of-action information, including genotoxicity (literature up to November 2013). The conclusions reached by the NRC-committee were practically the same as those by NTP (2014). For nasopharyngeal cancer the evidence was judged to be strongest, with the population-based case-control study for occupational exposure by Vaughan et al. (2000) as the most informative study. The NCI-industrial cohort study of mortality was considered an important additional source of evidence. Despite the low number of cases in this study, because of the high quality of the study and the fact that all cases were highly exposed the overall results were considered persuasive. For sinonasal cancer in humans the committee concluded that there was positive evidence from several population-based case-control studies. The studies in which no association was found were considered too small in size for this rare tumour type. For leukemias the committee identified a number of strong and moderately strong studies, based on which it concluded that overall the epidemiologic studies provided evidence of a causal association between formaldehyde and myeloid leukemia in humans. An important issue is how such tumours could arise given the portal-of-entry reactivity of formaldehyde. The NRC-committee concluded that there

was considerable evidence for relevant mechanistic events beyond the portal of entry, which included genotoxicity and mutagenicity, hematologic effects, and effects on gene expression (NRC 2014).

### *4.2.2 Mode of action including genotoxicity*

US-EPA (2010), RAC (2012), NTP (2014) and NRC (2014) provide in depth reviews of the large body of data on this topic. Below the conclusions drawn in these reviews are briefly summarised.

The mutagenic and genotoxic potential of formaldehyde has been examined in numerous studies, including in vitro studies for several endpoints (gene mutations, chromosome aberrations, micronuclei etc.), in vivo studies in animals and humans both at the site of contact and at systemic sites.

RAC (2012)
The RAC reviewed the available mutagenicity data and reached the following conclusions for the various categories of tests:

- in cultured mammalian cells and in cultured human cells: positive for chromosomal aberrations, micronucleus formation and sister chromatid exchanges (SCE), positive for DNA-protein crosslinks (DPX) and DNA-adducts, contradictory results for gene mutations (HGPRT-assay, mouse lymphoma assay), conclusion: formaldehyde is an in vitro mutagen with a predominantly clastogenic mode of action;
- in vivo animals at site of contact: positive for induction of DPX in nasal mucosa cells of rats (≥0.3 ppm, ≥0.4 mg/m$^3$) and nasal turbinates of monkeys (≥0.7 ppm, ≥0.9 mg/m$^3$); results for clastogenic effects (chromosomal aberrations, micronucleus formation and sister chromatid exchanges) contradictory;
- in vivo humans at site of contact: contradictory results for induction of micronuclei in buccal and nasal mucosa cells
- in vivo animals at distant site: negative for DNA adducts or DPX in different organs, negative for DPX, SCE's or micronuclei in peripheral blood cells in rats after inhalation, positive results for these endpoints considered insufficiently reliable and/or biologically implausible
- in vivo humans at distant site: contradictory results for DPX, chromosomal aberrations, micronuclei and SCE's in human lymphocytes, biologically systemic effects are not expected because formaldehyde exposure does not lead to an increase in formaldehyde concentration in blood.

In addition, RAC (2012) attempted to identify key events in formaldehyde carcinogenicity at the site of contact of the upper respiratory tract (URT). The degree of evidence for a threshold type dose-response was reviewed, taking into account the conclusion of the Dossier submitter that experimental results and mechanistic data did indeed support such a dose-response, with cytotoxicity-induced cell proliferation being the predominant feature in the carcinogenic process. Summary of RAC conclusions:

- in animal inhalation bioassays increases in cell proliferation, precursor lesions and tumour response occurred at ≥2 ppm (≥2460 µg/m$^3$);
- but dose-related non-significantly increased cell proliferation has also been observed at <2 ppm (<2.4 mg/m$^3$);
- the enhancing effect of marked cytotoxicity-induced cell proliferation in the URT explains the steep upward bend of the dose response curve for tumours at high concentrations in rats (>6 ppm, >7.4 mg/m$^3$);
- formation of DPX has been demonstrated at low concentrations, i.e. at ≥0.3 ppm, ≥0.4 mg/m$^3$ (rat) and ≥0.7 ppm, ≥0.84 mg/m$^3$ (monkey) (no data in humans);
- DPX at concentrations below those demonstrated to cause increased cell proliferation could induce mutagenic effects which in turn could lead to tumour formation;
- but the data are insufficient to show the presence or absence of mutagenic effects at low concentrations (<2 ppm, <2.5 mg/m$^3$) in response to persistent DPX-formation.

In its final conclusion on the mode-of-action, the RAC (2012) first notes that there are indications for a 'practical threshold' at 2 ppm, 2.5 mg/m$^3$ for cell proliferation and DPX formation, but then points out that data also indicate non-significant dose-related increases in cell proliferative activity and DPX formation below this level. Because of the overall limited database below 2 ppm, 2460 µg/m$^3$ RAC concludes that no firm conclusion can be drawn on the presence of a biologically meaningful threshold or the existence of linearity in the dose-response curve in the low dose range (<2 ppm, <2460 µmg/m$^3$) for both effects.

US-EPA (2010)

In its draft Toxicological Review of Formaldehyde US-EPA provides a comprehensive evaluation of all data on mutagenicity, genotoxicity and mode of action. Major conclusions on mutagenicity and genotoxicity are that formaldehyde:

- is a demonstrated in vitro clastogen (positive for chromosome aberrations, micronuclei, increase in small colony incidence in the Mouse Lymphoma Assay);
- primarily interacts with DNA by producing DPX, this has been demonstrated at the site of contact in vivo
- is likely clastogenic at the site of contact in vivo based on available tests in animals and humans;
- at distant site: several occupational studies found clastogenic effects in circulating lymphocytes but the data are not fully conclusive.

Major conclusions on the mode of action at the site of contact:

- formaldehyde has multiple modes of action each with its own dose response relation;
- formaldehyde directly reacts with DNA (primarily by DPX-formation) and this may lead to mutations (clastogenic action);
- only for the mode-of action of cytotoxicity-induced cell proliferation the data indicate a threshold; this threshold is primarily relevant for the tumours seen in animal bioassays but less so for humans because they are exposed to much lower concentrations;

- of the various modes of action identified, direct formaldehyde genotoxicity and resulting mutation, inhibition of DNA repair and formaldehyde-induced cell proliferation in conjunction with mutation may be operative and relevant to human exposures at exposure levels resulting in minimal tissue flux (i.e. below the threshold for cytotoxicity-induced cell proliferation).

Conclusion mode of action for distant site:

- leukemia induction as found in epidemiology studies could be due to bone marrow toxicity, direct or indirect action on hematopoietic stem cells at the site of contact or on immune cells at the site of contact, URT-infection and/or viral reactivation may play role;
- further research needed to evaluate these possible modes of action.

IARC (2012)

In its evaluation of formaldehyde carcinogenicity IARC (2012) concluded that available data strongly indicate that genotoxicity plays an important role in the carcinogenicity of formaldehyde in nasal tissues in humans, and that cellular replication in response to formaldehyde-induced cytotoxicity promotes the carcinogenic response. For the induction of leukaemias three possible mechanisms were identified each of which involved genotoxicity but further research was deemed necessary to determine which mechanism is most important (IARC 2012).

NRC (2014)

NRC also extensively reviewed the large data base for formaldehyde on mutagenicity, genotoxicity and mode of action. Major conclusions:

- there is strong evidence that formaldehyde induces DNA adducts, crosslinks, strand breaks, mutations and clastogenic damage (SCEs, micronuclei) in in vitro systems;
- portal of entry sites in vivo: positive for DNA damage in animals, positive for DPX-formation in animals, positive and negative (contradictory) for strand breaks, mutations, micronuclei and chromosome aberrations in animals, 11/14 studies positive for micronuclei in humans;
- overall: genotoxic and mutagenic mode of action is supported by the experimental evidence, negative studies notwithstanding the evidence is consistent strong and specific (NRC 2014).

### *4.2.3 Quantitative cancer risk assessment*

The mode of action for tumour formation is crucial for how the cancer risk is to be assessed quantitatively. As explained above, in most past evaluations (RIVM, WHO, etc.) the available evidence was concluded to support a non-linear, threshold dose response for the induction of tumours in the URT by formaldehyde. Because of the threshold, preventing the relevant precursor event of local cytotoxicity in the upper airways will simultaneously preclude any risk for tumour formation. Sensory irritation as observed in volunteer studies was taken as a surrogate for local cytotoxicity and a derivation based on the maximum concentration not producing sensory irritation led to a result that was

considered to also be protective against the carcinogenic effect by formaldehyde. Most recently this approach has been adopted by WHO (2010) in the derivation of the indoor air quality guideline for formaldehyde and it was also proposed within REACH by the dossier submitter. This led to a proposed limit of 100 µg/m3 (30-minutes value), which was derived from human volunteer studies on sensory irritation and which was also concluded to pose no extra cancer risk for the general population.

As will be clear from the previous paragraphs, whether a threshold exists in the local tumorigenic action of formaldehyde in the URT is a complex issue. That the dose response relation shows a steep bend upwards at relatively high exposure concentrations (> 6 ppm, >7.5 mg/$m^3$;) due to cytotoxicity-induced cell proliferation is not controversial. This discontinuity explains the high incidences of squamous cell carcinomas in rat inhalation studies. For the lower concentration range, however, the balance of evidence is much more difficult to determine. On crucial points the data show contradictions and limitations that at present cannot be resolved. In its review of this issue RAC (2012) concluded that that no firm conclusions can be drawn on the presence of a biologically meaningful threshold or the existence of linearity in the dose-response curve in the low dose range. But other agencies, i.e. IARC and several US agencies (EPA, NRC, NTP) conclude that the balance of evidence clearly indicates a genotoxic and mutagenic mode of action. Based on this US-EPA chose a non-threshold approach in its draft Toxicological Review form 2010.

Because of this uncertainty about the mode of action at low concentrations, quantitative cancer risk assessment is explored further below, based on both animal data and available human data.

4.2.3.1 QCRA based on animal data

Formaldehyde induces high incidences of tumours (squamous cell carcinomas) in the nasal cavity of rats after long-term inhalation, as was shown in several studies. Conolly et al. (2004) developed a biologically-based dose response model (BBDR) for extrapolating the tumour data from two studies in F344 rats by Kerns et al. 1983 and Monticello et al. 1996, respectively, to humans. US-EPA (2010) provides an in depth analysis of this BBDR-model, concluding that although the model provided a more accurate and biologically based description of the dose-response in the range of the available data (than purely statistical descriptions), variations of the model described the data just as well, and when the model variations were used for extrapolating to environmental exposure concentrations for humans, the calculated risk levels varied widely and no relevant biological input data were available that could provide constraint on the model outcomes. US-EPA concluded that the BBDR-model thus cannot be characterized as a plausible upper bound approach in the face of model uncertainties (which was the claim by Conolly et al. 2004). Accordingly, US-EPA only used the BBDR-model to derive the POD in the range of the observed data but did not use it to extrapolate far below the observed data. As potential POD's the upper bound extra risks of 0.005 and 0.01 were calculated ($BMDL_{0.5}$ and $BMDL_{1.0}$). The inhalation unit risk for squamous cell carcinomas in the human respiratory tract (upper and lower) was then derived by linear

extrapolation to the origin from the POD. The unit risk denotes the extra lifetime cancer risk per unit of lifetime exposure (µg/m$^3$ or ppm). Thus, for instance a unit risk of $10^{-5}$ per µg/m$^3$ means that lifetime exposure to 1 µg/m$^3$ in air is associated with an extra lifetime cancer risk of $10^{-5}$ (=0,001%). This implies that of 100,000 individuals exposed to 1 µg/m$^3$ during their entire lifetime 1 would be expected to develop cancer.
The unit risk estimation for formaldehyde based on the rat nasal tumour data by US-EPA included the calculation of the human equivalent concentration (HEC) by assuming that continuous lifetime exposure to a given steady-state flux of formaldehyde (expressed in pmol/mm$^2$-hour) leads to an equivalent risk of nasal cancer across species. The risk per respiratory or transitional epithelial cell with replicative potential was calculated as a function of formaldehyde flux in the nasal region in rats and then extrapolated to the nasal region of humans and subsequently to the rest of the respiratory tract of humans. The latter extrapolation, however, turned out not to contribute significantly to the unit risk calculated for humans (> 97% of the unit risk in humans was associated with the upper respiratory tract).Thus, a $BMDL_{0.5}$-value of 0.410–0.435 ppm (0.510 – 0.530 mg/m$^3$) and a $BMDL_{1.0}$-value of 0.430–0.460 ppm (0.530 – 0.560 mg/m$^3$) were derived as POD's. Linear extrapolation from these BMDLs led to unit risks of $1.2x10^{-2}$ (derived from the $BMDL_{0.5}$) and $2.2x10^{-2}$ per ppm lifetime exposure (derived from the $BDML_{1.0}$) (US-EPA 2010).

4.2.3.2 QCRA based on human data

US-EPA (2010) chose the NCI cohort study as the basis for quantitative cancer risk estimation for cancer of the nasopharynx (NPC). Consisting of 25,619 workers (88% male) employed in 10 plants prior to 1966, this study was the largest of the three independent industrial worker studies and was the only one with sufficient individual exposure data for exposure-response modeling. A follow-up through 1994 presented exposure-response analyses for nine NPC deaths based on 865,708 person-years of follow-up.[3] The NCI cohort study included a detailed exposure assessment for each worker based on exposure estimates for different jobs held and tasks performed. Quantitative exposure estimates were generated for each worker using several different metrics—peak exposure, average intensity, cumulative exposure, and duration of exposure. For the NPCs significant trends were observed for the cumulative and peak exposure metrics. Based on cumulative exposure as the dose metric, the 95% lower confidence limit of the concentration associated with an extra risk for NPC mortality of 0.05% ($LEC_{0.005}$) was calculated.[4] Using incidence data from US cancer registry,

[3] In 2010 (the time of writing the US-EPA draft) a more recent follow-up for these tumours in the NCI-cohort was not yet available. Such a follow-up was published in 2013, showing up one extra NPC-death, leading to a total of 10 extra NPC-deaths for 998,239 person-years of follow-up (Beane Freeman et al. 2013, Mortality from solid tumors among workers in formaldehyde industries: An update of the NCI cohort. Am. J. Ind. Med., 56: 1015–1026)

[4] US-EPA typically uses an extra risk of 1% as the POD for epidemiologic data to avoid upward extrapolation. For NPC, however, even the 1% level of risk is associated with Relative Risk (RR) estimates that are substantially higher than those actually observed in the pivotal epidemiology study. Hence, even a 1% extra risk level would be an upward extrapolation. Based on the life-table program, the RR estimate for an extra risk of 1% for NPC mortality would be as high as 46. Even 0.1% yields an RR estimate on the high end of the observable range of the NCI cohort epidemiology study (RR = 5.5). A 0.05% extra risk level yields an RR

the associated $LEC_{0.005}$ for total NPC incidence was calculated, leading to a value of 0.045 ppm (55 µg/m$^3$). From this value a unit risk of $1.1x10^{-2}$ per ppm lifetime exposure was derived via linear extrapolation (US-EPA 2010).

US-EPA (2010) also derived unit risks for Hodgkin lymphoma (27 deaths) and leukemia (123 deaths) mortality based on the NCI-cohort study (using the 2009 follow-up for these neoplasms for this cohort).

estimate of 3.27, which better corresponds to the RRs in the range of the data. Thus, 0.05% extra risk was selected for determination of the POD.

# 5 Update of the MPR-air

## 5.1 5.1. Short term celling value (30 min)

As explained in previous chapters the critical short-term effect by formaldehyde is sensory irritation. For protection against this effect a value of 100 µg/m$^3$ as a 30-minutes average has been established for indoor air by WHO (2010) based on the study with human volunteers by Lang et al. (2007). This value is close to the existing Dutch value for indoor air of 120 ug/m$^3$ (30 minutes average) which was based on a 1974 study among volunteers in a medical anatomical preparation room. The value of 100 ug/m$^3$ (30 minutes average) has also been proposed as DNEL by the registrant in REACH.

## 5.2 5.2 MPR year average

As explicitly stated by WHO its indoor air quality guideline of 100 µg/m$^3$ is a ceiling value that should not be exceeded during any 30-minutes period during the day. With a view to possible exceedance, it is important to note that in measuring formaldehyde in indoor or outdoor air the usual sampling times are considerably longer than 30 minutes. As can be seen from the information in chapter 3, typically average concentrations over 24 or 48 hours or over one or even two weeks are measured. Given the continuous nature of most sources for indoor emission (particle board, carpets etc.) in combination with relatively limited air flow indoors, concentration fluctuations during the day will most likely be limited in indoor environments. Accordingly, for indoor air comparing concentrations measured over 48 hours or even 1- or 2-week periods with the 30-minutes limit probably will not carry the risk that that the limit inadvertently will be exceeded during any 30 minutes' period within the total sampling time. For outdoor air, however, concentrations fluctuate over the day, as concentration measurements show. This point was already discussed in the proposals for ambient air limits by the Gezondheidsraad in 1984. Thus, as the Gezondheidsraad argues, for outdoor air complying with the 30-minutes ceiling of 100 or 120 ug/m$^3$ necessitates using a lower limit as the 24-hours average. Based on the outdoor air concentration data then available the Gezondheidsraad proposed a maximum of 40 µg/m$^3$ for the 98$^{th}$ percentile of the distribution of 24-hour average concentrations and a maximum of 30 µg/m$^3$ for the 95$^{th}$ percentile. These proposals by the Gezondheidsraad, however, have not officially been adopted as MPR-values by the former Ministry of Public Health and the Environment. Possibly the current MPR-air of 10 µg/m3 as a year-average was promulgated instead, with this figure for the year-average being the result of a similar line of reasoning and thus being primarily based on information on the distribution of formaldehyde outdoor air concentrations (again on the condition that the 30-minutes ceiling value of 120 µg/m$^3$ should not be exceeded).

As discussed in Chapter 4 uncertainties exist with regard to the carcinogenic effects by formaldehyde. Several human epidemiological studies indicate an increased risk for (myeloid) leukemia after inhalation

exposure to formaldehyde. Because formaldehyde is highly reactive chemically it will react locally in the upper airways, which notion is supported by findings in numerous animal studies. In view of this, RAC (2012) considers the induction of leukemia by formaldehyde via inhalation biologically implausible and stresses that the effect was absent in the relevant animal studies carried out with formaldehyde. IARC and US-agencies (US-EPA, NTP, NRC), however, consider the epidemiological evidence on this point to indicate a causal link. Additional research to explain the mechanism by which inhaled formaldehyde could induce this kind of tumours (i.e. at a distant site) could clarify this issue. For the MPR-air this effect will not be considered further.

For the induction of tumours of the upper respiratory tract after inhalation of formaldehyde it is unclear whether a threshold exists in the low concentration range (i.e. the level to which humans may be exposed in practice). As discussed above, on crucial points the data show contradictions and limitations that at present cannot be resolved. For the MPR air year-average value a non-threshold calculation is carried out below.

Non-threshold evaluation as developed by US-EPA led to unit risks for the induction of cancer in the nasopharynx of $1.2\times10^{-2}$ – $2.2\times10^{-2}$ per ppm (based on animal data) and $1.1\times10^{-2}$ per ppm (based on human data).

From the unit risks the concentration associated with the extra cancer risk level defined as the MPR within the Dutch Environmental policy, i.e. the risk of $10^{-6}$/year (equivalent to about $10^{-4}$/lifetime) can be calculated. The unit risk of 0.011 (1.1%) denotes the extra risk per life for lifetime exposure to 1 ppm (1.25 mg/m$^3$). The lifetime exposure concentration associated with a lifetime extra risk of 0.0001 (=MPR) will be 110 times (=0.011/0.0001) lower than 1 ppm (1.25 mg/m$^3$). Similarly based on the unit risk of 0.022 (2.2%) the MPR concentration will be 220 times lower than 1 ppm (1.25 mg/m$^3$). Thus, based on the unit risks of 0.011 and 0.022, the concentrations associated with the extra cancer risk level of the MPR are equal to:
- 1.25 mg/m$^3$/110 = 0.011 mg/m$^3$ ≈ 10 µg/m3
- 1.25 mg/m$^3$/220 = 0.00568 mg/m3 ≈ 6 µg/m$^3$.

Cancer registration data for the Netherlands show a total incidence of 75 cases of nasopharyngeal cancer for the year 2012 (as reported in Globocan 2012). This equals an incidence of 4 per million per year (based on a total population of 17 million). If actual exposures of the Dutch population to formaldehyde are at 6-10 µg/m$^3$ as a lifetime average[5], the level which is associated with an extra cancer risk of 1 per million per year, one in four actual cases of nasopharyngeal cancer would be attributable to formaldehyde exposure.

[5] The mean lifetime exposure concentration for the whole Dutch population is unknown but such a figure could be a reasonable approximation given the information in Chapter 3.

Thus, non-threshold extrapolation to the cancer risk level defined as the MPR based on the available cancer unit risks leads to a result close to existing MPR-air of 10 $\mu g/m^3$. Because the available evidence is uncertain on the point of formaldehyde acting via a non-threshold or threshold mode of action, this result is relevant and supports keeping the existing year-average MPR-air in place.

# 6 Conclusion

The current update formaldehyde leads to unchanged values for the MPR-air:

| | |
|---|---|
| Proposed year-average: | 10 µg/m$^3$ |
| Proposed short-term ceiling (30 minutes): | 120 µg/m$^3$ |

The year-average value supersedes the RIVM (1995) value of 1.2 µg/m$^3$.

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## Appendix 1: General population limit values for formaldehyde since the mid 1980's

RIVM (1995)
In 1995 formaldehyde inhalation toxicity was re-evaluated by the RIVM. It was noted that in monkeys increased nasal discharge was found at ≥240 µg/m$^3$ (exposure for 22 hours/day, 7 days/week for 26 weeks, study by Rusch et al. 1983). It was also noted that a similar LOAEL for nasal irritation was found in studies in humans as reported by the Gezondheidsraad (1984). In the latter studies transient nasal, throat and eye irritation was present at this level, whereas at 120 µg/m$^3$ no such effects were found (Gezondheidsraad, 1984). From this NOAEL of 120 µg/m$^3$ an MPR-air (TCA) of 1.2 µg/m$^3$ was calculated by using an uncertainty factor of 100 for inter-individual variability and extrapolation from short- to long-term exposure (RIVM 1995).

ATSDR (1999)
For non-cancer endpoints ATSDR derived the following health-based reference values (Minimal Risk Levels, MRLs). For acute exposures (≤14 days) ATSDR derived an MRL of 0.04 ppm (50 µg/m$^3$). This was based on mild eye, nose, and throat irritation at 0.4 ppm observed in some human subjects in a volunteer study by Pazdrak et al. (1993) in which the subjects were exposed for 2 hours. An uncertainty factor of 9 was used, 3 for the use of a minimal LOAEL and 3 for human variability. For intermediate exposure (15-365 days) an MRL of 0.03 ppm (35 µg/m3) was derived from an NOAEL of 0.98 ppm for clinical signs of nasopharyngeal irritation (hoarseness and nasal congestion and discharge) and lesions in the nasal epithelium (squamous metaplasia and hyperplasia), as observed in Cynomolgus monkeys exposed to formaldehyde for 22 hours/day, 5 days/week for 26 weeks (Rusch et al. 1983). The NOAEL was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability). For chronic exposure an MRL of 0.008 ppm (10 µg/m3) was derived. This was based on a minimal LOAEL of 0.24 ppm for histological changes (loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia replacing the columnar epithelium) in nasal tissue specimens from a group of 70 workers employed for an average 10.4 years (range 1–36 years) in a chemical plant that produced formaldehyde and formaldehyde resins for impregnating paper (study by Holmstrom et al. 1989). The LOAEL was divided by an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 for human variability) (ATSDR (1999, 2010)[6].

WHO (2000)
WHO (2000) derived an ambient air quality guideline for formaldehyde of 0.1 mg/m$^3$ based on the occurrence of signs of irritation of nose and throat above this level in healthy subjects (volunteer studies). To prevent significant sensory irritation in the general population, an air quality guideline value of 0.1 mg/m$^3$ as a 30-minute average was

[6] In 2010 ATSDR prepared an addendum to its Toxicological Profile form 1999. It is stated in this addendum that the MRLs are under review pending the review by the National Research Council of the Draft US-EPA IRIS Toxicological Review from 2010.

recommended. Because this was over one order of magnitude lower than the presumed threshold for cytotoxic damage to the nasal mucosa, this guideline value was concluded to represent an exposure level at which there would be a negligible risk of upper respiratory tract cancer in humans.

Health Canada (2005)
In 2005 Health Canada updated its indoor exposure guideline for residential air quality. For eye irritation as the most sensitive effect seen in several chamber experiments in human volunteers, an NOAEL and an LOAEL of 615 and 1,230 µg/m3 respectively, were selected based on the study by Kulle (1993) in which healthy subjects were exposed for 3 hours. A short-term (1-hour average) guideline value of 123 µg/m3 (100 ppb) was proposed, equalling one tenth of the lowest concentration at which eye irritation was reported by Kulle (1993). Epidemiological studies indicated that formaldehyde at lower levels than 123 ug/m3 is linked to effects on lung function/asthma in children after chronic exposure. Two individual studies reported no effect at measured concentrations of 10 to 29 µg/m3 and 30 to 49 µg/m3, respectively, a non-significant increase of risk at 50 to 59 µg/m3 (OR 1.2) and a significantly increased risk at 60 µg/m3 (OR 1.39, $p<0.05$). Based on this a long-term exposure guideline of 50 ug/m3 (as an 8-hour average) was recommended. The risk of cancer was concluded to be negligible at formaldehyde concentrations sufficiently low to prevent local irritation and inflammatory responses in the upper airways (Health Canada 2005).

BfR (2006)
Prompted by a revaluation of formaldehyde carcinogenicity by IARC in 2004, BfR reassessed formaldehyde cancer data and derived a safe level in air. Inhalation of formaldehyde leads to formation of DNA-protein-crosslinks (DPX) at the anatomical site of exposure. Tumour formation by formaldehyde was concluded to be linked to, first, a local cytotoxic effect which triggers reactive cell proliferation and, second, a change in genetic information. Regenerative cell proliferation increases the number of DNA replications and thus increases the probability of a DPX initiated DNA replication error resulting in a mutation. Given this sequence of steps the threshold for the induction of cytotoxicity was concluded to represent a "practical threshold" for increased cancer risk. In rats local cytotoxicity is seen at ≥2 ppm (≥2.4 mg/m3). For humans an NOAEL for cytotoxicity cannot be derived due to lack of data and sensory irritation was used as a surrogate. Based on chamber studies and occupational data BfR derived an estimated NOAEL for sensory irritation in humans of 0.1 ppm (0.12 mg/m$^3$). This level was considered the safe level for the general population (BfR 2006).

OEHHA (2008)
OEHHA (2008) derived Reference Exposure Levels (RELs) for 1-hour duration (for intermittent 1 hour exposures), for 8 hours duration (for repeated 8 hour exposures) and for chronic exposure. The 1-hour REL was based on an NOAEL of 0.5 ppm (0.6 mg/m$^3$) for eye irritation from the human volunteer study by Kulle et al. (1987), in which healthy subjects were exposed for 3 hours (LOAEL in this study 1 ppm). From the study results, a $BMCL_{05}$ for eye irritation of 0.44 ppm (530 µg/m$^3$)

was derived. The latter level was divided by uncertainty factor of 10 for intraspecies differences in toxicodynamics. This increased factor was chosen because the respiratory irritant effect by formaldehyde has the potential to exacerbate asthma in the sensitive subpopulation of infants and children. The result was a 1-hour REL of 50 µg/m$^3$.
The 8-hours REL and the chronic REL were numerically identical. This value of 9 µg/m$^3$ was derived based on an NOAEL of 0.09 mg/m$^3$ from an occupational study by Wilhelmsson and Holmstrom (1992), in which effects on the upper airways of workers exposed to a mean formaldehyde concentration of 0.26 mg/m$^3$ during working hours (5 days/week) were compared with a referent group exposed to 0.09 mg/m$^3$. The critical effects in this study included nasal obstruction and discomfort, lower airway discomfort, and eye irritation. The average exposure period was 10 years (range 1-36 years). The REL was obtained by applying an uncertainty factor for intraspecies differences in toxicodynamics of 10 (the same factor as applied for the 1-hour REL) to the NOAEL of 0.09 mg/m$^3$ (OEHHA 2008).

WHO (2010)
In an evaluation specifically aimed at indoor air contaminants, WHO (2010) derived an indoor air quality guideline for formaldehyde. From its review of volunteer studies and other dose response data pertaining to sensory irritation in humans after acute or subacute exposure, WHO (2010) concluded:

- the lowest concentration at which human volunteers subjectively reported sensory irritation is 0.38 mg/m$^3$ for 4 hours (from the study by Lang et al. 2008);
- increases in eye blink frequency and conjunctival redness as detected in the same study mark the threshold for trigeminal stimulation of the eyes; for this effect the NOAEL was 0.6 mg/m$^3$;
- there is no indication of accumulation of effects over time with prolonged exposure;
- the perception of odour may result in some individuals reporting subjective sensory irritation, and individuals may perceive formaldehyde at concentrations below 0.1 mg/m$^3$. However, this is not considered to be an adverse health effect.

The NOAEL of 0.6 mg/m$^3$ for the eye blink response (obtained from the volunteer study by Lang et al. 2007) was adjusted using an assessment factor of 5 derived from the standard deviation of nasal pungency (sensory irritation) thresholds, leading to a value of 0.12 mg/m$^3$, which was rounded down to 0.1 mg/m$^3$. Neither increased sensitivity nor sensitization is considered plausible at such indoor concentrations in adults and children. This value is considered valid for short-term (30-minute) duration; this threshold should not be exceeded at any 30-minute interval during the day.

As to the carcinogenic effect of formaldehyde in the nasal cavity in animals and in the nasopharynx in humans, WHO (2010) concluded that there is sufficient evidence for a non-linear, biphasic concentration–response relationship. For increased cell proliferation as the identified key event for tumour development, the long-term NOAEL was concluded to be 1.25 mg/m$^3$ in rats. A threshold approach based on this NOAEL would lead to a proposed guideline of 0.21 mg/m$^3$ for the protection of

health for long-term effects, including cancer. WHO adds that alternative approaches based on a biologically motivated model by Conolly et al (2004) led to estimated additional cancer risks of $2.7*10^{-8}$ for continuous lifetime exposure to 0.125 mg/m$^3$ and $10^{-6}$ or less for non-smokers continuously exposed to 0.25 mg/m$^3$. Given these results it was concluded that use of the short-term (30-minute) guideline of 0.1 mg/m$^3$ will also prevent against long-term health effects, including cancer.

US-EPA (2010) (Draft)

In a comprehensive data evaluation US-EPA (2010) identifies a number of candidate human studies for deriving a non-cancer RfC. This was done for the following endpoints: sensory irritation, upper respiratory tract pathology, induction of asthma and atopy, pulmonary function, reproductive and developmental effects and effects on immune function. The derivation led to candidate RfCs ranging from 2.8 to 70 ppb (3.4 – 84 µg/m$^3$). In addition US-EPA quantified formaldehyde cancer risks for nasopharyngeal cancer, Hodgkin lymphoma and leukemia based on human data, yielding unit risks (per ppm lifetime exposure) for extra cancer incidence of $1.1*10^{-2}$, $1.7*10^{-2}$ and $5.7*10^{-2}$, respectively. US-EPA also provides an in depth discussion of the biologically-based dose response model (BBDR) developed by Conolly et al. (2004) for formaldehyde human cancer risk assessment based on the nasal tumours as found in rat studies. The conclusion by US-EPA is that due to model uncertainties the human cancer risk estimates obtained by applying this model cannot be characterised as a plausible upper bound cancer risk estimate in the low dose range. Instead US-EPA opts for linear extrapolation based on two Points of Departure (POD) derived using the BBDR model, i.e. an extra risk of 0.5% and an extra risk of 1%. Linear extrapolation from these PODs led to unit risks of $1.2*10^{-2}$ (for POD 0.5%) and $2.2*10^{-2}$ (for POD 1%) (US-EPA 2010).

ANSES (2012)

Mandin et al. (2009, 2012) report the results of a risk assessment for the French general population that included exposure assessments for acute and chronic exposure situations and a selection of appropriate health-based reference values. In the dose-effect relationship for formaldehyde carcinogenicity in the upper respiratory tract, irritation was considered the key precursor event for nasopharyngeal cancer with necrosis-cytotoxicity, cellular proliferation and genotoxicity as successive key events. The hypothesis of a threshold for tumour formation in the upper respiratory tract was accepted although it was pointed out that uncertainty remains as to the dose response curve in humans at concentrations below 1.24 mg/m$^3$ (the LOAEL for nasal tumours in rats). Existing health-based reference values values as derived by ATSDR, OEHHA and BfR were reviewed, leading to the selection of 10 µg/m$^3$, as proposed by ATSDR, as the chronic air quality guideline for all indoor environments (excluding occupational settings) to protect the general population, including susceptible subgroups, from the irritant effects of long-term exposure. For acute exposure the 1-hour acute reference exposure level (REL) of 94 µg/m$^3$ as proposed by the (OEHHA 1999) and the 14 days MRL of 50 µg/m$^3$ as proposed by ATSDR (1999) were selected as the appropriate reference values. Based on the

latter value an indoor air quality guideline of 50 µg/m$^3$ (as a 2-hour average) was established (Mandin et al. 2009, 2012).[7,8]

REACH (2012)
Within REACH the lead registrant proposed a general population DNEL (Derived No-Effect Level) based on the German occupation limit of 0.3 ppm. Using an assessment factor of 3 would lead to a general population DNEL of 0.1 ppm (1.2 mg/m$^3$). In the Draft Substance Evaluation Report (SEV) as prepared by the Dutch member state competent authority (RIVM 2012) this DNEL was discussed and provisionally accepted for preliminary risk evaluation.

[7] Actual indoor air quality guidelines values proposed can be found at: [ HYPERLINK "https://www.anses.fr/fr/system/files/AIR2011sa0123.pdf" ]
[8] The implementation of the French indoor air quality guidelines for chronic exposure to formaldehyde involves a phased approach with an interim guideline of 30 µg/m3 applying from 1-1-2015 onwards and a value of 10 µg/m3 from 1-1-2023 onwards. ([ HYPERLINK "https://www.anses.fr/fr/system/files/AIR2011sa0123.pdf" ])